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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53 (c).

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☐ *Additional inventors are being named on the ___ separately numbered sheets attached hereto*

TITLE OF THE INVENTION (280 characters max)

DRUG DELIVERY DEVICE

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ENCLOSED APPLICATION PARTS *(check all that apply)*

☒ Specification *Number of Pages* 9 ☐ Small Entity Statement

☒ Drawing(s) *Number of Sheets* 1 ☐ Other (specify)

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT *(check one)*

☒ A check or money order is enclosed to cover the filing fees

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The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☒ No.

☐ Yes, the name of the U.S. Government agency and the Government contract number are: _____

Respectfully submitted,

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Date 6/4/99

REGISTRATION NO. *(if appropriate)* 26,723

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USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT

This collection of information is required by 37 CFR 1.51. The information is used by the public to file (and by the PTO to process) a provisional application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 8 hours to complete, including gathering, preparing, and submitting the complete provisional application to the PTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, Washington, D.C., 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Box Provisional Application, Assistant Commissioner for Patents, Washington, D.C., 20231.

DRUG DELIVERY DEVICE

FIELD OF THE INVENTION

The present invention relates to electrically mediated transport of drugs into tissue and/or into cells of the tissues.

BACKGROUND OF THE INVENTION

Electroportation is a technique used for introducing molecules across a cell membrane and into a cell. In a typical application, a cell culture is mixed with a target molecule and a brief electrical field is applied to the mixture. The electrical field causes a transient porosity of the cell membranes, allowing the molecules to enter the cell. U.S. Patent 5,501,662, the disclosure of which is incorporated herein by reference, describes an electroportation system for blood, in which an electric field is applied to a vessel having blood cells mixed with a target gene (or other molecules) and the electric field causes the genes to be transported into the cells. Electroportation is especially useful for large molecules, such as proteins, and for other molecules which do not have a biological mechanism for crossing the cell barrier.

Ionophoresis is a method of transporting drugs into a body tissue, from outside the body tissue, usually from the skin. The drug is provided in a charged form and, when an electric field is applied, the electric field moves the charged drug along the gradient of the field.

PCT publication WO98/15317, the disclosure of which is incorporated herein by reference, describes an implantable drug-eluting tip which uses a cardiac pacing signal to cause charged drug particles to leave a reservoir and be available locally. It is suggested in that publication that the electric field of the pacing is sufficient to ionophorese the drug into the heart tissue. Injection of DNA into individual cells is suggested using a similar device, for apply toxins to tumor cells, apparently not in the heart. However, it is not clear whether the fields strengths and durations of a pacing signal are sufficient for electroportation or even ionophoresis for any considerable depth.

SUMMARY OF THE INVENTION

One aspect of some preferred embodiments of the invention relates to using a non-excitatory pulse to control molecule availability in the heart. The control may include one or more of causing a molecule to exit a reservoir, ionophoresis of the molecule into cardiac tissue and/or electroportation of the molecule into individual cardiac cells. As used herein the term "non-excitatory pulse" means an applied electric field which does not induce a propagating action potential in the heart, for example due to its frequency, polarity, waveform, duration, amplitude and/or its being applied at a time in the cardiac cycle when the local heart tissue does not respond to the pulse. As used herein the term molecule means any type of molecule, including, especially,

genetic material, such as DNA and RNA, genetic vectors, such as viruses and plasmids, polypeptides, hormones and small molecule drugs. In addition, the molecules may include ATP, cAMP and/or particles having the molecule adsorbed thereto or located inside a volume of a hollow particle.

In a preferred embodiment of the invention, knowledge of what types of pulses will not cause a fatal arrhythmia and/or methods for controlling such arrhythmia should they occur are used to apply pulses having larger voltages, currents and/or durations than previously thuoght possible, to the heart, for the purpose of transporting drugs. In addition, a variety of waveforms becomes available. Preferably, apparatus designed for non-excitatory pulses is used and not a pacemaker, again, making possible various programmable pulse forms and larger amounts of power.

In a preferred embodiment of the invention the type of electrode used is a point electrode, a line electrode, a wide area electrode, a coronary electrode which is inserted into a coronary vessel and/or a one- or two- dimensional matrix electrode.

In a preferred embodiment of the invention, the molecules are provided by the electrode, for example using a drug-eluting electrode as known in the heart. Alternatively or additionally, the molecule is provided in other ways, for example the molecule is injected or applied using an implanted pump (possibly with output ports at the region to be treated or in a vascular bed thereof or adjacent thereto where the electrical pulse can transport it). Possibly, a decomposing matrix having the molecule embedded therein is used to supply the molecule. Alternatively, the molecule is ingested.

In a preferred embodiment of the invention the molecule and the non-excitatory signal cooperate to have a desired, synergistic effect on the heart, for example the molecule enhancing a contractility increasing effect of the molecule or the signal enhancing a contractility increasing effect of the molecule. Alternatively, the signal may be selected to have a minimal effect on the heart.

An aspect of some preferred embodiments of the invention relates to using non-ionized/charged molecules for electrically mediated transport in the heart. Preferably, the effect of electroportation is achieved by the electric field of the non-excitatory signal momentarily opening pores in the cardiac cell membranes.

An aspect of some preferred embodiments of the invention relates to a method of treating a cardiac dysfunction. In a preferred embodiment of the invention, a patient is temporarily connected to a device that electrically transports molecules into cardiac tissue. Possibly, the device also

performs monitoring functions and/or provides other treatment, such as applying electrical fields that prevent fatal arrhythmia or pacing the heart.

An aspect of some preferred embodiments of the invention relates to treating coronary blood vessel or other vessels that are near the heart, using electrically mediated molecule transport. In a preferred embodiment of the invention, the timing and/or other parameters of application of electric fields for transporting the molecules are selected to not have a pro-arrhythmic effect on the heart. In a preferred embodiment of the invention the molecule transported is one which causes breakdown of clots or other occlusions, which causes angiogenesis and/or which prevents stenosis or re-stenosis of the vessel. It is noted that pacemaker lead placement usually avoid place the lead over a coronary vessel, in order to provide better electrical contact with the heart.

An aspect of some preferred embodiments of the invention relates to using a non-excitatory pulse generating device to both transport a molecule and determine an affect of the molecule, for example an effect on conduction velocity, contractility or action potential propagation. Alternatively or additionally, to measuring the effect, the device can be used to counteract or block pro-arrhythmic effects of the molecule and/or of the pulse used to transport the molecule. Alternatively or additionally, the device is used to determine when and what type of drug should be applied.

An aspect of some preferred embodiments of the invention relates to providing one or more types of molecules at a plurality of locations on the heart. In a preferred embodiment of the invention, the amount of molecule transported and the type of molecule transported at each point is individually controllable. Alternatively or additionally, the application regimen may be pre determined. Alternatively, the application regimen may be varied, for example in response to needs of the heart or in response to the effect of a previous application. Preferably, a non-excitatory pulse is used to transport the molecule.

An aspect of some preferred embodiments of the invention relates to synchronizing the transport of a molecule with cardiac activity, for example the cardiac cycle or cardiac output variations caused by activity, to achieve desirable effects, especially transport effects. In one example, the molecule is transported when it will have the greatest effect on the heart. In another example, the molecule is transported when travel through the heart tissue is easiest, for example when the muscles of the heart are relaxed. Possibly, the non-excitatory pulse is used to extend the cardiac cycle to allow the molecule to travel further in one cardiac cycle.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a schematic illustration of a heart connected to a non-excitatory signal providing device, in accordance with a preferred embodiment of the invention.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

Fig. 1 is a schematic illustration of a heart 102 connected to a non-excitatory signal providing device 100, in accordance with a preferred embodiment of the invention. Device 100 is operative to provide non-excitatory signals to the heart and/or otherwise control the heart, as a hole or in portions thereof. In a preferred embodiment of the invention, some or all of the non-excitatory signals generated by device 100 are used to transport a molecule into the heart tissue or surround tissues, where application of an electrical field might adversely affect the heart. The transport mechanism may be that of removing the molecule from a reservoir using an electric field, ionophoresis into the heart and/or electroportation into the cardiac cells themselves. The mechanism actually used depends on the geometry of the device (e.g., the existence and type of molecule reservoir), the charge of the molecule and the characteristics of the electric field.

Fig. 1 illustrates several types of electrodes, including a line electrode 112, a point electrode 114, a coronary electrode 108, implanted in a coronary and having a plurality of point electrodes along it, and a mesh electrode 106. Not shown are other suitable electrodes, such as intra-muscular electrodes. Depending on the type of transport, the field may be very localized, such as a large voltage different between two adjacent point electrodes (or mesh vertexes). Alternatively, the field may be less-localized, such as between an entire mesh and the casing of device 100.

The molecule may be provided at the electrode itself, using any of the many methods known in the art. Additionally, the molecule may be provided using a tube 118 to a vascular bed of the treated area or adjacent the treated area. In some cases, the electrode lead itself (indicated by reference 104) is hollow or can other wise be used to provide a molecule. Possibly, the electrical signals are used to advance the molecule lead. Preferably, the electrical transportation is used to move the molecule to the treated area. Possibly, ionophoresis is used to attract the drug to the electrode rather than to push it away as usually in the art.

In a preferred embodiment of the invention, device 100 includes an input for indicating when a drug is injected or otherwise provided into the user, so that the application of the non-excitatory signal can be timed to when the drug (or other molecule) is available at the electrodes.

Apparatus suitable for performing the function of device 100 and non-excitatory signals are described, for example in PCT application IL97/00012, the disclosure of which is incorporated herein by reference.

In a preferred embodiment of the invention, device 100 is implantable. Alternatively, device 100 is external, possibly also the electrodes being external. In a preferred embodiment of

the invention, the external device is used for a short term treatment, such as for gene therapy, for recovery from surgery or for recovery from a serious arrhythmia or acute ischemic event.

The ability to use a non-excitatory signal rather than a pacing signal results in a much wider range of relevant molecules and treatment possibilities. The following table compares a typical pacemaker and a non-excitatory signal provider in accordance with preferred embodiments of the invention:

Characteristic	Pacemaker	Non-excitatory device
Field basis	Voltage	Current or voltage
Amplitude	5-8 Volts, 2mA	0-40V, 50mA
Duration	0.05-2 ms	1-1000 ms
Effective impedance	500-1500 ohm	240-700 ohm
Polarity	Usually mono-phasic	Arbitrary
Waveform	Usually decaying square pulse	Arbitrary

As a result of the freedom in choosing the field basis, various types of transport effects can be achieved, for example voltage based effects and charge based effects.

The available amplitude makes it easier to transport large molecules, provide deep tissue ionophoresis or even electroportation. The available durations complement the available power levels by allowing a much longer transport time. The use of large electrodes and mesh electrodes allows the local treatment of many locations in the heart and/or the treatment or large areas of the heart, which is not possible using a pacing lead. Also, this lowers the impedance of the electrode.

It should be noted that the molecules may be transported during any part of the cardiac cycle, to take advantage of (or avoid) particular electrochemical and/or physiological conditions. If the electroportation method is ionophoresis it may be necessary to use charged molecules, molecules witch can be charged or dipole-charged by the field or to adsorb the molecule to a charged particle.

In a preferred embodiment of the invention, the non-excitatory signal has a synergistic interaction with the molecule. In one example, the non-excitatory signals are used to prevent or block an arrhythmia caused by the molecule or by the electrical field used to transport the molecule. In another example, the molecule is used to undo adverse effects of the non-excitatory field, for example inhibition or over-sensitizing of cells at the fringes of the field. In another example, such as for the molecule caffeine, the non-excitable signal enhances the effect of the molecule. In another example, the non-excitatory signal is used to extend the cardiac cycle, to temporarily de-sensitize a portion of the heart and/or to stop blood flow to a portion of the heart, so

as to allow more time for the transport of the molecule or to provide better physical parameters for the transport.

In a preferred embodiment of the invention, device 100 is programmed or otherwise controlled to provide a desired spatial and temporal regimen to the heart. Such a regimen can include an indication which part of the heart is treated with which drug and/or electrical field for what duration and under what circumstances. One or more sensors 116 (in some cases the electrodes can double as sensors) may be used to provide an indication of the heart's current status or its response to certain treatments. By suitable control of the electrical signals, a reservoir based technique can be used to selectively elute drugs, when needed. Further, due to the increased control over the electrical signals, it is possible to selectively eject one of several drugs from a reservoir. As known in the field of gel electrophoresis, some molecules move better in AC fields and some better in DC fields. In addition, the polarity of the field, its frequency and/or amplitude may have an effect on the transport of the molecule. By providing a sufficiently thick barrier on the reservoir and suitably applying a field, only a selected one of several molecules will be able to leave. This type of methodology may also be used to provide a certain molecule to a certain depth in the heart tissue. For example, a train of low power pulses may be used to ionophoretically transport a drug and then a high voltage pulse is used to open cell pores so that the drug (or other molecule) can enter the cell. Also, in this way the tissue level to which the drug is to be provided can be controlled. By using local electrodes, the arrival of the molecules at the desired tissue level can be monitored as well. Alternatively or additionally, by transporting radioactive or other marker drugs, it is possible to image or otherwise view the tissue and determine which cells were affected.

In a preferred embodiment of the invention, selective molecule providing is used to control the heart locally and/or for temporally short periods, such as seconds or tens of seconds. This effect is achieved by selectively transporting fast acting drugs to target tissues, in shor times and without substantially providing the drugs to nearby tissues. Alternatively or additionally, this affect is achieved by electrically de-sensitizing neighboring tissue from responding to the drugs.

Local control of the heart can also have a global effect, for example, controlling an AV conduction velocity will affect the entire behavior of the heart.

In a preferred embodiment of the invention, electroportation techniques are sued to provide gene therapy to the heart. In gene therapy, genetic material or a carrier thereof, such as plasmids, artificial chromosomes or viruses are provided into a cell. Examples of suitable genetic material include, anti-sense DNA, RNA and poly-peptides to block the expression of genes which have an undesirable effect. The provided genetic material may be used for various purposes, including

curing a genetic defect or a viral disease, causing a cell to differentiate in a desired manner or changing the function of a cell. In one example, a heart is remodeled, by providing genetic material or other molecules which cause certain parts of the heart to atrophy or enlarge. In another example, the activation of the heart is modeled, for example by causing a cell type, such as an AV node cell, to increase its conduction velocity, for example by suitable over-expression or under-expression of certain ion pumps or channels. Other cell parameters which may be change din this method include sensitivity (to hormones electrical signals and/or other feedback loops in the heart), plateau duration, excitation window duration and self-pacing rate (SA node).

In another example, a long QT syndrome patient is treated by causing the expression of suitable ion channels or pumps to those cells that require it. This expression can be caused by providing the gene that creates the channels or creates a protein that transports them to the cell membrane, as well as by blocking a gene which stops the production.

It should be appreciated that diffusion of drugs and other molecule sin the heart may be enhanced by diffusion between cardiac muscle cell groups, in which the cell ends are fused together.

In a post ischemic-event treatment application, drugs for maintaining the dilation of blood vessels or drugs for reducing oxygen requirements may be applied. In addition, molecules damaged or destroyed by the ischemic event may be provided by electrical transport techniques.

In an angiogenesis application, hormones and/or other angiogenesis factors are electrically transported to ischemic tissue and/or other tissue in the heart to cause increased blood vessel generation.

In an organ transplant application, electrical transport methods are used to provide anti-rejection drugs or immune system inhibition drugs to a transplanted heart.

In a slow ablation application, a drug which suspend activity of a heart cell is applied to points of a mesh electrode, the electrode having a desired effect is used to provide a killing dose of the same drug or of a different drug. Alternatively, selective ablation is possible even without first determining the effect of a "suspending" drug.

In a coronary vessel application, ionophoresis and electroportation become possible in blood vessels which are near excitable tissue, such as the heart. Example treatments include anti-clotting drugs, drugs to prevent re-stenosis, drugs to prevent stenosis and gene therapy to convert the blood cells to those having a desired function, such as excretion of a desired anti-clotting factor. In the case of blood vessels, the electric field may be applied using a suitable stent or to augment the behavior of a stent which needs to be implanted. Such a stent may include a power

supply and sensing electronics. Alternatively, the power is provided by wireless means or by wired means, such as electrodes.

It will be appreciated that the above-described methods of transporting molecules in the heart and nearby tissues may be varied in many ways. In addition, a multiplicity of various features, both of methods and of devices has been described. It should be appreciated that different features may be combined in different ways. In particular, not all the features shown above in a particular embodiment are necessary in every similar preferred embodiment of the invention. Further, combinations of the above features are also considered to be within the scope of some preferred embodiments of the invention. Also within the scope of the invention are devices and/or software for programming existing devices to make the device comply with the methods described herein. When used in the following claims, the terms "comprises", "includes", "have " and their conjugates mean "including but not limited to".

It will be appreciated by a person skilled in the art that the present invention is not limited by what has thus far been described. Rather, the scope of the present invention is limited only by the following claims.

CLAIMS

1. A method of transporting a molecule into cardiac tissue, comprising:
providing a molecule at the cardiac tissue; and
applying a non-pacing signal to transport the molecule into the tissue.

2. A method according to claim 1, wherein said molecule comprises genetic material.

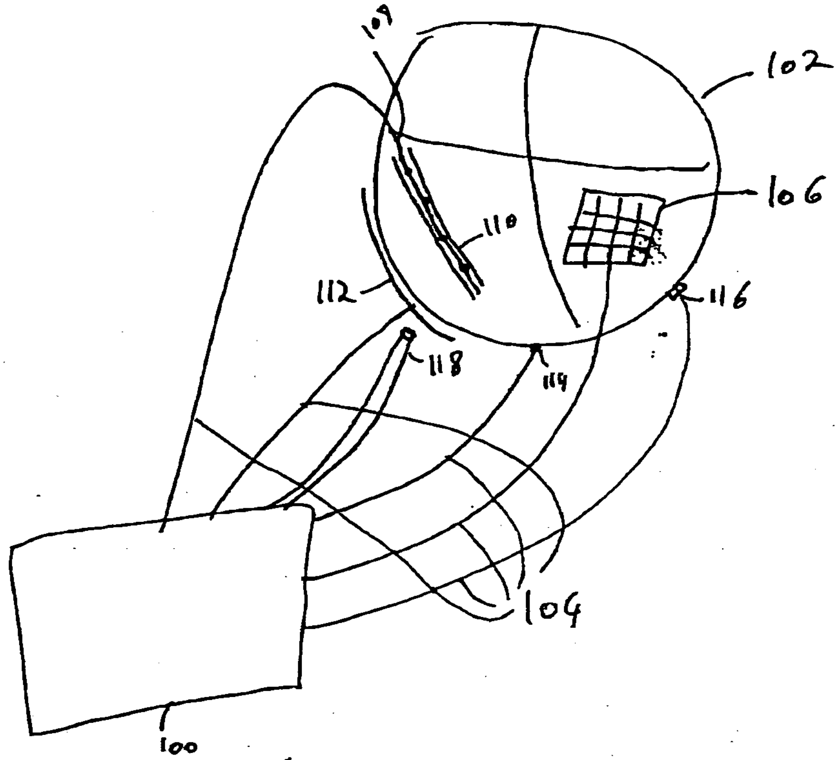

Fig. 1